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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☐ THE PERIOD FOR RESPONSE:

a) ☐ is extended to run _____ or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☒ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 11/13/2001 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☒ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☒ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☒ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☒ They raise the issue of new matter. (See Note).

   d. ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: See enclosed note

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, the proposed amendment ☐ will be entered ☒ will not be entered and the status of the claims will be as follows:

   Claims allowed: None
   Claims objected to: w/in
   Claims rejected: 37, 39, 159-161, 165, 167

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because the rejections as enunciated in the previous Office Action and applied to the claims under consideration are maintained for reasons of record.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☒ Other See enclosed note

RONALD B. SCHWADRON
PRIMARY EXAMINER
GROUP ~~1800~~ 1700

PTOL-303 (REV. 5-89)

REJECTION OF CLAIMS 37, 39 and 159-161 UNDER 35 U.S.C. § 103(a)

Claims 37, 39 and 159-161 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Seder *et al.*, 1993, PNAS, USA, 90:10188-10192in view June *et al.* (WO 94/29436) or June *et al.* (USP 5,858,358) and Carew (USP 5,123,901) and Nabel *et al.*, 1987, Nature, 326(6114):711-713. This rejection is respectfully traversed.

Teachings of the cited references and differences from the instant claims

Seder *et al.*

Seder *et al.* teaches that naive $CD4^+$ T cells produce IL-2, but little or no IFN-γ, and states that *in vitro* they develop into producers of IL-4 or IFN-γ depending upon the conditions of the priming culture. Using TCR transgenic $CD4^+$ cells, Seder *et al.* presents studies that examine the role of IL-12 and IL-4 in antigen-specific priming. Seder *et al.* teaches that IL-12 enhances the ability of cells to develop in IFN-γ producers upon restimulation. Seder *et al.* concludes that Il-12 has a major effect on the inductive phase of T-cell priming by enhancing commitment to IFN-γ production. It is respectfully submitted that nowhere does Seder *et al.* teach any information regardeing Th1 cells, except to state that the results indicate that the cytokines present at the outset of a response powerfully determine the character of the ensuing response, suggesting that (page 10192):

> ...optimal vaccine strategies for protection against intracellular organisms might include both administration of IL-12 and neutralization of IL-4. **A major question that remains open** is whether established Th1 or Th2 phenotypes can be altered by manipulations of the cytokine environment. (emphasis added)

Therefore, the only information Seder *et al.* discloses regarding Th1 cells is the equivocal conclusion that it is not clear whether Th1 and Th2 phenotypes can be altered. Thus, Seder *et al.* does not suggest production of compositions of predominantly Th1 cells, and certainly does not provide any motivation to produce high densities of Th1 cells in excess of 10^{10} cells/liter. Seder *et al.* when describing therapeutic protocols merely suggests a vaccine containing IL-12 and

an IL-4 neutralizing agent. Therefore, Seder *et al.* is deficient by failing to suggest compositions that contain clinically relevant amounts of Th1 cells.

Secondary references

The teachings of the secondary references are set forth above in the rejection of the same claims citing O'garra as the primary reference.

There would have been no motivation to have combined the teachings of Seder *et al.* with June *et al.*, Carew and Nable, and the combination does not result in the instantly claimed methods

Seder *et al.* is merely directed to assessing the role of cytokines in determining T-lymphocyte function and concludes that the ability to alter phenotype is unresolved. Seder *et al.* does not suggest preparing large quantities of Th1 cells nor any therapeutic or other use thereof. In fact, each raises a doubt whether such cells can be produced. Since Seder *et al.* does not provide a reason to generate large quantities of T cells, much less Th1 cells, there would have been no motivation to have combined the teachings of Seder *et al.* with those of June *et al.*, Carew and Nabel *et al.*

The secondary references: June *et al.* is directed to methods for expansion of cells, but does not suggest expansion of one type of cell for any purpose, nor the expansion of cells to a density in excess of 10^{10} cells/liter. As discussed above, the cells produced by the method of June *et al.* are clearly not predominantly Th1 cells. The cytokine profile of the resulting cells (Table 2) is clearly that of a mixed population. Carew is directed to a perfusion-based method of removing pathogens from body fluids, and Nabel *et al.* teaches that compounds that activate lymphocytes can induce production of HIV from latently infected cells. Thus, Nabel *et al.* is merely directed to an observation.

Moreover, none of the art of record provides any uses for expanded compositions of predominantly Th1 cells. Thus, there is nothing in the teachings of the secondary references and Seder *et al.* that would have motivated combination of their teachings nor that would have motivated one of ordinary skill to produce a predominantly Th1 cell population in excess of 10^{10} cells/liter.

The combination of references does not result in the claimed subject matter

Seder *et al.* concludes that the ability to manipulate T cell phenotype is unclear, and neither provides a clear procedure for doing so. Seder does not teach or suggest that compositions containing predominantly Th1 cells of any T-cell subset population, including $CD4^+$ cells can be produced. Moreover, Seder *et al.* does not contemplate any therapeutic methods that require administration of cells.

None of the secondary references teaches or suggests preparation of compositions of predominantly Th1 cells in excess of 10^{10} cells/liter. Accordinaly, it is respectfully submitted that the combination of cited references do not teach, suggest or result in differentiation of mononuclear cells to predominantly Th1 cells and the expansion of Th1 cells *in vitro* to produce compositions containing clinically relevant numbers of Th1 cells in excess of 10^{10} cells/liter, as required by Applicant's claims. Moreover, with respect to dependent claims, the combination of references do not disclose or suggest a density of more than 10^8 cells/ml of predominantly Th1 cells. Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

The Rejection over Seder *et al.* in view of June *et al.*, Carew and Nable, is Based on Improper Use of Hindsight.

It is respectfully submitted that the Examiner has combined the teachings of the prior art with those of the instant application. Only the instant application that suggests altering immune balance by administering compositions of either Th1 or Th2 cells; none of the cited references provide such suggestions. It is the instant application that teaches and shows that it is possible to selectively expand Th1 cells to clinically relevant numbers and it is the instant application that provides the motivation to do so. None of the cited references suggests a therapeutic appraoch in which compositions of predominantly Th1 cells are prepared in the amounts and densities claimed.

Therefore, the Examiner has failed to set forth a prima facie case of obviousness. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS 165 and 167 UNDER 35 U.S.C. § 103(a)

Claims 165 and 167 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over O'garra *et al.*, 1994, Current Opinion in Immun., 6:458-466 in view June *et al.* (WO 94/29436) or June *et al.* (USP 5,858,358) and Carew (USP 5,123,901) and Nabel *et al.*, 1987, Nature, 326(6114):711-713as applied to claims 37, 39, 159-161 above, and further in view of Cracauer *et al.* (USP 4,804,628). This rejection is respectfully traversed.

The Claims

Claims 165 and 167 are directed to method claims 37 and 39, respectively, wherein cell expansion is effected in a hollow fiber reactor.

Teachings of the cited references and differences from the instant claims

As set forth above, combination of O'garra *et al.*, June *et al.*, Carew and Nable does not teach or suggest activating and differentiating mononuclear cells to predominantly Th1 cells and expansion of the Th1 cells to an excess of 10^{10} cells/liter.

Cracauer *et al.*

Cracauer *et al.* teaches a hollow fiber cell culture device that includes a hollow fiber cartridge having a shell and a plurality of capillaries extending through the shell with at least some capillaries having semi-permeable walls. A cell culturing space is located between the shell and the capillaries. The device includes a chamber containing a second medium supply fluidly connected to the cell culturing space.

Cracauer *et al.* does not teach or suggest use of its hollow fiber cell culture for growing clinically relevant numbers of any type of lymphoid cell, much less Th1 cells, as required in Applicant's claims. The device of Cracauer *et al.* is not

taught to be suitable for growing lymphoid cells at densities exceeding 1 x 10^{10} cells/liter.

The Examiner has failed to set forth a case of *prima facie* obviousness

(1) There would not have been motivation to have combined the teachings of O'garra *et al.*, June *et al.*, Carew and Nable with those of Cracauer *et al.*

As set forth above, the combination of O'garra *et al.*, June *et al.*, Carew and Nable does not teach or suggest activating and differentiating mononuclear cells to predominantly Th1 cells and expansion of the Th1 cells to an excess of 10^{10} cells/liter, and thus, provides no motivation to have selected the device of Cracauer *et al.* Cracauer *et al.* provides no suggestion for growing T lymphoid cells, much less Th1 cells, in its device. Therefore, one of ordinary skill would not have been motivated to expand differentiated Th1 cells in the device of Cracauer *et al.*

(2) The combination of references does not result in the claimed subject matter

As discussed above, the combination of O'garra *et al.*, June *et al.*, Carew and Nable fails to teach or suggest a differentiating mononuclear cells into Th1 cells prior to expansion, as required in the pending claims. In addition, the combination of O'garra *et al.*, June *et al.*, Carew and Nable does not teach or suggest Th1 cell growth to produce high cell density that exceed 1 x 10^{10} cells/Liter.

Cracauer *et al.* does not cure the deficiencies in the teachings of the primary references because Cracauer *et al.* merely teaches a hollow fiber device. There is no teaching or suggestion in Cracauer *et al.* to use the device for expanding T cells at high cell density nor how to adapt the device to achieve such a goal. Further, Cracauer *et al.* does not teach or suggest a method for producing regulatory cells nor the step of effecting differentiation prior to expansion.

Therefore, Cracauer does not cure the deficiencies in the teachings of O'garra *et al.*, June *et al.*, Carew and Nable, and the combination of references does not teach or suggest the instantly claimed methods. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS 165 and 167 UNDER 35 U.S.C. § 103(a)

Claims 165 and 167 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Seder *et al.*, 1993, PNAS, USA, 90:10188-10192in view June *et al.* (WO 94/29436) or June *et al.* (USP 5,858,358) and Carew (USP 5,123,901) and Nabel *et al.*, 1987, Nature, 326(6114):711-713as applied to claims 37, 39, 159-161 above, and further in view of Cracauer *et al.* (USP 4,804,628). This rejection is respectfully traversed.

The Claims

Claims 165 and 167 are directed to method claims 37 and 39, respectively, wherein cell expanxion is effected in a hollow fiber reactor.

Teachings of the cited references and differences from the instant claims

As set forth above, the combination of Seder *et al.*, June *et al.*, Carew and Nable does not teach or suggest activating and differentiating mononuclear cells to predominantly Th1 cells and expansion of the Th1 cells to an excess of 10^{10} cells/liter.

Cracauer *et al.*

As set forth above, Cracauer *et al.* does not teach or suggest use of its hollow fiber cell culture for growing clinically relevant numbers of any type of lymphoid cell, much less Th1 cells, as required in Applicant's claims. The device of Cracauer *et al.* is not taught to be suitable for growing lymphoid cells at densities exceeding 1×10^{10} cells/liter.

The Examiner has failed to set forth a case of *prima facie* obviousness

(1) There would not have been motivation to have combined the teachings of Seder *et al.*, June *et al.*, Carew and Nable with those of Cracauer *et al.*

As set forth above, combination of Seder *et al.*, June *et al.*, Carew and Nable does not teach or suggest activating and differentiating mononuclear cells to predominantly Th1 cells and expansion of the Th1 cells to an excess of 10^{10} cells/liter, and thus, provides no motivation to have selected the device of Cracauer *et al.* Cracauer *et al.* provides no suggestion for growing T lymphoid cells, much less Th1 cells, in its device. Therefore, one of ordinary skill would not have been motivated to expand differentiated Th1 cells in the device of Cracauer *et al.*

(2) The combination of references does not result in the claimed subject matter

As discussed above, the combination of Seder *et al.*, June *et al.*, Carew and Nable fails to teach or suggest a differentiating mononuclear cells into Th1 cells prior to expansion, as required in the pending claims. In addition, the combination of Seder *et al.*, June *et al.*, Carew and Nable does not teach or suggest Th1 cell growth to produce high cell density that exceed 1×10^{10} cells/Liter.

Cracauer *et al.* does not cure the deficiencies in the teachings of the primary references because Cracauer *et al.* merely teaches a hollow fiber device. There is no teaching or suggestion in Cracauer *et al.* to use the device for expanding T cells at high cell density nor how to adapt the device to achieve such a goal. Further, Cracauer *et al.* does not teach or suggest a method for producing regulatory cells nor the step of effecting differentiation prior to expansion.

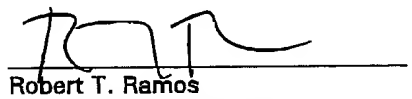
Therefore, Cracauer does not cure the deficiencies in the teachings of Seder *et al.*, June *et al.*. Carew and Nable, and the combination of references does not

teach or suggest the instantly claimed methods. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & MCAULIFFE LLP

By: 
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: MICHEAL L. GRUENBERG

Serial No.: 09/127,411

Filed: July 31, 1998

For: AUTOLOGOUS IMMUNE CELL THERAPY: CELL COMPOSITIONS, METHODS AND APPLICATIONS TO TREATMENT OF HUMAN DISEASE

Art Unit: 1644

Examiner: Schwadron, R

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Commissioner for Patents
Washington, D.C. 20231, on this date.

10/24/01
Date

Robert T. Ramos

MARKED UP CLAIMS (37 C.F.R. § 1.121)

Please cancel claims 36, 155, 156, 157, 158, 159 and 162.

Please amend claims 37, 38, 39 and 154, as follows:

37. (Three Times Amended) **[The method of claim 36]** A method of producing virally purged CD4+ cells, comprising:

(a) **collecting** mononuclear cells from a patient infected with HIV;

(b) contacting the cells with mitogenic antibodies to induce cell activation;

(c) selecting CD4+ cells that are HIV- after activation; and

(d) inducing cell proliferation and expanding the selected cells to in excess of 1 x 10^{10} cells **per liter**, wherein:

cell proliferation and expansion is performed in the absence of exogenous interleukin-2 (IL-2), wherein, in the contacting step, the activation of the cells occurs under conditions that promote Th1 cell differentiation to produce a population of cells that contains predominantly Th1 cells.

38. (Three Times Amended) The method of claim [36] 37, further comprising:

after selecting CD4+ cells that are HIV- and prior to expanding the selected cells, growing a plurality of aliquots in the presence of mitogenic agents;

selecting from the aliquots those that are HIV-; and

then expanding the selected cells to in excess of 1×10^{10} cells per liter.

39. (Twice Amended) The method of claim [36] 37, wherein the cells are activated with anti-CD3 monoclonal antibodies in the presence of interferon-γ (IFN-γ).

154. (Amended) The method of claim [36] 40, wherein cell expansion is effected in a hollow fiber bioreactor.